UNIVERSITY OF GONDAR

COLLEGE OF MEDICINE AND HEALTH SCIENCES

INSTITUTE OF PUBLIC HELATH

ASSESSMENT OF RELAPSE OF VISCERAL LEISHMANIASIS AND RISK FACTORS AMONG VISERAL LEISHMANIASIS PATIENTS IN WEST ARMACHIHO, NORTHWEST ETHIOPIA. INSTITUTION BASED RETROSPECTIVE STUDY.

BY:

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Acronyms and Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
CI	Confidence Interval
CD4	Cluster of Differentiation
CL	Cutaneous Leishmaniasis
DAT	Direct Agglutination Test
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
LD	Leishmaniasis Donovani
LC	Localized Cutaneous Leishmaniasis
MSF	Medicines San Frontiers
PLHIV	People Living with Human Immunodeficiency Virus
RDT	Rapid Diagnostic Test
SSG	Sodium stibogluconate
TB	Tuberculosis
TOC	Test of Cure
VCT	Voluntary Counseling and Testing
VL	Visceral Leishmaniasis
WHO	World Health Organization

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ABSTRACT

Introduction: Leishmaniasis has been associated with poverty and also believed to constitute a serious impediment to socioeconomic development. The disease is endemic in the environment that ranges from deserts to rain forests in rural and urban settings in over 98 countries of the tropics, sub tropics, and southern Europe.

Objectives: To assess visceral leishmaniasis relapse rate among all visceral leishmaniasis patients in leishmaniasis treatment center at West Armachio, Northwest Ethiopia, 2014.

Methods: A five years institution based retrospective follow up study was conducted among 1510 VL patients who were enrolled in Leishmaniasis treatment center from January, 2009 to December 31, 2013. The information extracted on the patient records. The data transfers from excel to SPSS version 20 for analysis. Life table was used to estimate the cumulative VL relapse survival and Log rank tests to compare relapse survival probability curves between the different categories of the explanatory variables. Bivariate and multivariate Cox proportional hazards model were used to identify predictors.

Result: A total of 1676 charts reviewed, out of this 1510 patient records were included in the analysis. The median age of the study participant was 24 yrs. And a total of 235 VL relapse cases were observed during the follow up period. Hence, the overall incidence density of VL relapse was 10 per 10,000 Person months.

Those who were hemoglobin level >7mg/dl had late probability to develop leishmaniasis relapse than Hgb level less than 7 mg/dl with an (AHR 0.69, 95% CI 0.49, 0.97).and Patients who were taking Ambisone and Ambisone +Meltifocin had less likely to develop relapse than a patient taking SSG. (AHR 2.62 CI 95% 1.72, 3.97) and AHR3.92 CI 95%2.51, 6.12) respectively.

Discussion: the predictors that were significantly associated with increased risk of relapse were HIV/AIDS Sero status, advanced WHO clinical stage and, VL treatment, Discharge hemoglobin level and edema. All this predictors had already been identified in other studies.

Conclusion and Recommendation: Leishmaniasis prevention strategies need to be strengthened with early diagnosis and treatment as a recommended in national guideline.

1. Introduction`

1.1 Statement of the problem

Leishmaniasis has been associated with poverty and believed to constitute a serious impediment to socioeconomic development. The disease is endemic in environments that range from deserts to rain forests in rural and urban settings in over 98 countries of the tropics, sub tropics, and southern Europe (1).

The Visceral leishmaniasis (VL) and Cutaneous Leishmaniasis (CL) relapse/re-infection dichotomy is a major concern in patients with HIV/AIDS, who are at risk for opportunistic infections. In areas where the diseases are endemic, the rate of re-infections might be higher than estimated. This could lead physicians to believe that treatment for relapsed infection failed. In fact, the patient has a newly acquired infection. Therefore, the inability to distinguish relapses from re-infections might be an important impediment to the evaluation of leishmaniasis treatment protocols (2).

Changes in the environment (climate change, deforestation and unplanned urbanization), population movements between endemic and non-endemic zones, appearance of therapy-resistant strains and immune suppression, mainly due to malnutrition and co-infection with the human immunodeficiency virus (HIV),are among the factors believed to contribute to emergence and re-emergence of VL. (1).

Visceral Leishmaniasis is predominantly found in the lowlands with varying degrees of endemicity. It is estimated that the annual burden of VL ranges from 2,000 to 4,500 cases of the 350 million people at risk of the disease, globally an estimated 2 million new cases (1.5 million cases of CL and 500,000 cases of VL) occur annually, but only 600,000 cases were officially declared (1, 3).

According to the 2012 WHO global Leishmaniasis estimate, Ethiopia is one of the ten high burden countries for CL and VL, it is predominantly found in the lowlands with varying degrees of endemicity. Population movement, poverty and malnutrition associated with presence of the sand fly vector and reservoirs makes the study area one of the affected areas by Leishmaniasis, which is a major public Health problem (1, 4).

The number of cases occurring around the world is clearly far higher than officially reported, and the number of infections still (4-5 times) higher. The difficulty in estimating the case burden is due to several factors: great fluctuations in number of cases within short periods of time, focal distribution, and numerous cases undiagnosed, as well as, misdiagnosed, not reported often asymptomatic cases. Case notification is compulsory in only 30 of the 88 endemic countries (5).

The co-infection of leishmaniasis and HIV is emerging as a new and frightful disease and is becoming increasingly frequent. Cases have been reported in 25 countries and are currently considered an ominous threat in Spain, Italy, France and Portugal. In these countries up to 70% of adult cases of visceral leishmaniasis are associated with HIV infection and up to 9% of people with AIDS suffer from newly acquired or reactivated visceral leishmaniasis (6).

Severity of immune suppression, suggests that the patient has not responded adequately for treatment. Higher risk of relapse associated with treatment and patients with relapse may have died without reaching a treatment center And the recurrent attack of visceral leishmaniasis is a sign of advanced disease and is a risk factor for relapse and death. Hence, studying the relapse rate and factors of leishmaniasis among PLHIV will have a great importance for the healthcare system to making appropriate adjustments as a solution (1).

1.1. Literature review

1.1.1. Relapse

A recent evidence of study in Nepal suggests that a significant number of patients relapse 6–12 months post-treatment with mulitefosine and the relapse rates in immune competent patients of between 6.8% to 10.8% at 6 months respectively, and up to 20.0% at 12 months(7).

A study showed in India the relapse rates were similar for primary VL and VL relapse. CD4 counts ,200 cells/lL at 6 months after ART initiation were predictive of subsequent relapse(8).

Patients who relapsed showed poor CD4 cell count recovery while receiving ART. ART was partially protective against VL relapse (HR, 0.46; 95% CI, 0.26–0.82). However, 28% of first VL relapses while receiving ART occurred despite a CD4 cell count 1 200 cells/mL; in 5% of VL relapses, the CD4 cell count had been 1 200 cells/mL for 1 6 months. Factors associated with all-cause mortality among patients receiving ART were baseline CD4 cell count ! 100 cells/mL (HR, 3.20; 95% CI, 1.30–7.87) and VL episodes during follow-up (HR for 1 episode, 4.97 [95% CI, 2.09–11.86]; HR for 1 2 episodes, 3.22 [95% CI, 1.01–10.23 (6).

A study in India showed that CD4 cell counts of .250–300 cells/lL at 6 months after VL treatment seemed to be associated with a very low risk of subsequent relapse. Four of the eight patients developing VL relapse were patients with previous VL relapse and had received VL treatment (conventional amphotericin B) before the initiation of liposomal amphotericin B within the program. The mean CD4 cell counts at 6, 12, and 24 months after cART initiation were 187 (95% CI,153–221), 234 (95% CI, 164–303) and 261 (95% CI, 37–486) cells/lL, respectively (9).

Male patients had higher odds of relapsing (unadjusted odds ratio [UOR] 1.8; 95% CI 1.2–2.6) compared with female patients. Patients aged ,5 years (UOR 3.6; 95% CI 1.8–7.2) and 45 years (UOR 2.2; 95% CI 1.2–1.4) were more likely to relapse than patients aged 15 to 30 years. Factors not associated with relapse in the univariate analysis (P- value.0.05) (10).

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In South Asia is currently the main focus for VL in the world, accounting for 67% of the total leishmaniasis disease burden. In 2005 Bangladesh reported 7,000 cases, India re-ported 32,800, and Nepal reported 3,000, . from 2001 to 2005, 16,210 cases of VL were reported in Brazil, and 315 (2%) patients were co-infected with HIV Of the co-infected patients, 78% were male, and the median age was 38 years (86% of patients were in the 20- to 49-year age group); 56.3% of the HIV infections were attributed to heterosexual transmission, and 53% and 29% of the cases were reported from the northeastern and southeastern regions, respectively. The clinical forms found among co infected cases are 43% MCL, 37% VL, and 20% CL (9).

A study conducted in Sudan revealed 18 (15.1%) relapsed within 6 months of treatment; 63 (52.9%) within 6–12 months; and 38 (31.9%) 12 months after treatment. A Higher odds of relapse compared with size 0 (odds ratio (OR) = 4.40 (95% CI 1.74–11.08), P = 0.002).17-days SSG/PM was associated with 2-fold higher odds of relapse (OR = 2.26 (1.46–3.51), P, 0.001) compared with 30-day SSG monotherapy. Test-of-cure of data were available for only 4.2% (7/166) of relapse patients who had a previous treatment record vs. 5.4% (431/7,924) of patients with no record of subsequent relapse (P = 0.6). None of the final test-of-cure results for relapse patients, and only 3/431 of the test-of-cure results for patients with no record of subsequent relapse were positive (10).

A study conducted in Ethiopia showed that test for cure was not routinely performed on all patients and therefore relapse and cure rate could not be established with certainty. As the patients did not receive secondary prophylaxis, many relapsed; the probability of relapse at 12 months was estimated to be about 70%.Baseline CD4 + cell count! 100 cells/mL, tuberculosis co-infection, and previous VL episodes were all risk factors for VL relapse. Among patients who received ART, CD4+ cell count reconstitution was blunted among those with multiple relapses of VL, compared with patients who did not have a VL relapse. A patient with baseline CD4 + cell count! 100 cells/mL and 3 previous VL episodes would have a 56% chance of relapsing within 1 year. Such patients might then be eligible for secondary prophylaxis (e.g.,

with pentamidine). It is not yet clear after what VL disease–free interval or at what CD4+cell count level patients are free of significant risk of VL relapse (6).

A study showed in Ethiopia VL relapse was more common among HIV-positive patients (40.5%) than among HIV-negative patients (10.6%). Among HIV-positive patients, relapse patients had larger spleens and were more malnourished compared with primary VL patients. rescue treatment of HIV-positive patients with Ambisome treatment failure increased the overall cure rate from 59.5% to 82.6%, but mortality in patients retreated with SSG was high (15.5%), often due to SSG toxicity (11).

A study showed in Tigray showed that The median age of the 791 cases of visceral leishmaniasis was 25 years (10 months to 77 years). More than three-quarters of the cohort were aged between 15 and 45 years. The male to female ratio was 11:1; females were younger than males, with 42% of the females (27/64) younger than15 compared to 9% of the males (68/722, $P < 0.001$ (12).

A study showed in Humera the adjusted hazard ratios for the effects of ART, baseline CD4 + cell count 100 cells/mL, and previous episodes of VL on the primary and secondary outcomes. ART had a protective effect on single or multiple relapses of VL. A patient with baseline CD4 + cell count 100 cells/mL and previous VL episodes would have a 56% chance of relapsing within 1 year (13).

The study confirms that patients with HIV／VL co-infection in Ethiopia had poorer response rates to anti-leishmaniasis treatment and increased mortality. Patients with HIV–VL co-infection were significantly less likely to have a positive outcome than HIV-negative patients (68.5% vs. 94.5%, $P < 0.001$). The presence of TB and sepsis syndrome also remained significant in the multivariate analysis as independent factors in HIV co-infected patients with VL (AOR 4.52, 95% CI 1.47–13.92 and 9.06, 95% CI 2.16–37.97, respectively)In a retrospective comparative study of 73 HIV-positive and 39 HIV-negative Spanish patients with VL, 90% of HIV-negative patients responded to treatment compared to only 54.8% of HIV-positive patients(14).

Another study conducted in India showed that male patients had higher odds of relapsing (unadjusted odds ratio (UOR) of 1.8; 95% CI 1.2-2.6) compared with

female patients. Patients aged, 5 years (UOR 3.6;95% CI 1.8-7.2) and 45 years (UOR 2.2;95% CI 1.2-1.4) were more likely to relapse than patients aged 15 to 30 years. The same study showed that CD4+ cell percentage and absolute count measured in the second VL relapse were found to be relatively low (22% and 450/ μm^3, respectively) (22% and 450/μm^3, respectively). However, even in PLHIV with CD4+ cell counts reaching 250 to 300/μm^3 the risk of relapse seems to be low (15).

WHO guide lines revealed that multiple episodes of relapsing VL in an older patient. Beyond the known decreased capacity of cytotoxic responses during senescence, no other immune-suppressing factor was identified in our case. CD4+ cell percentage and absolute count measured in the second VL relapse were found to be relatively low (22% and 450/µm, respectively). However, even in human immunodeficiency virus cases(PLHIV) with CD4+ cell counts reaching 250 to 300/ µm the risk of relapse to the best of our knowledge, there are very few reports of relapsing VL in the immune competent in the literature (15) (10).

Another study also showed that patients who exhibited a decrease in spleen size of 0.5 cm/day by the time of discharge appeared to have higher odds of relapse (1.7; 95% CI 1.1–2.5) compared with those who exhibited a decrease in spleen size of .0.5 cm/day. No other clinical factors were significantly associated with risk of relapse. Notably, nutritional status, spleen size and Hb level upon admission, and duration of treatment were not predictive of relapse. Relapse rates in immune competent patients between 6.8% to 10.8% at 6 months respectively, and up to20.0% at 12 months in Nepal (10).

A study conducted in Sudan revealed that the larger spleen size upon admission and at the time of discharge were strongly associated with relapse, as was treatment with short-course combination treatment(17 days sodium stibogluconate /paromomycin vs. 30 days sodium stibogluconate). Age, sex, nutritional status, mobility, and treatment complications were significantly associated with relapse(2). The study confirms that patients with HIV/VL co-infection in Ethiopia had poorer response rates to anti Leishmaniasis treatment and increased mortality. positive

outcome was achieved in 94.5% of HIV negative patients compared to only 68.5% of co-infected patients. In a retrospective comparative study of 73 HIV positive and 39 HIV negative Spanish patients with VL, 90 % of HIV negative responded to treatment compared to only 54.8 % of HIV positive patients. There was also a three times higher mortality rate in HIV positive than HIV negative patients(17.5% vs. 5.4%) (16).

A study In Ethiopia Splenomegaly on admission may indicate severity of illness, parasite burden, and degree of immune suppression. The prevalence of triple co-infection (VL, HIV, and tuberculosis) among HIV-positive VL patients in our study was 29.7%, similar to that observed in another Ethiopian study A total of 130／137 (94.9%) of HIV-negative and 65／69 (94.2%) of HIV-positive patients with haemoglobin measurements were anaemic. Total white cell and platelet counts were available for 118 and 105 HIV-negative patients and 51 and 39 HIV-positive patients. Thrombocytopenia was more commonly seen in HIV-negative than co-infected patients (90.5% v 76.9%, OR = 2.85, 95% CI 1.06–7.67, P = 0.038 (17).

Another study in shows that there was no difference in initial cure rate between the miltefosine group (88.3%; 95% CI, 84.0%–91.7%) and the SSG group (87.6%; 83.2%–91.2%) (P-value 0.90). However, initial treatment failure with survival was more Frequent in the miltefosine group (7.9% in the miltefosine group vs. 0.7% in the SSG group; OR, 12.4;), whereas mor- P ! .0001 mortality was lower in the miltefosine group (2.1% in the miltefosine group vs. 9.7% in the SSG group; OR, 0.20;). P-value .0002. the independent risk factors for death were determined to be receiving SSG rather than miltefosine (OR,6.53; 95% CI, 2.53–16.89), being HIV-infected or having an unknown HIV status (OR, 3.54; 95% CI, 1.25–10.06), and vomiting (OR, 2.97; 95% CI, 1.28–6.87). Other risk factors for death (age, body mass index, hemoglobin level, diarrhea, and inability to walk unaided) were interdependent (18).

1.2. Conceptual frame work

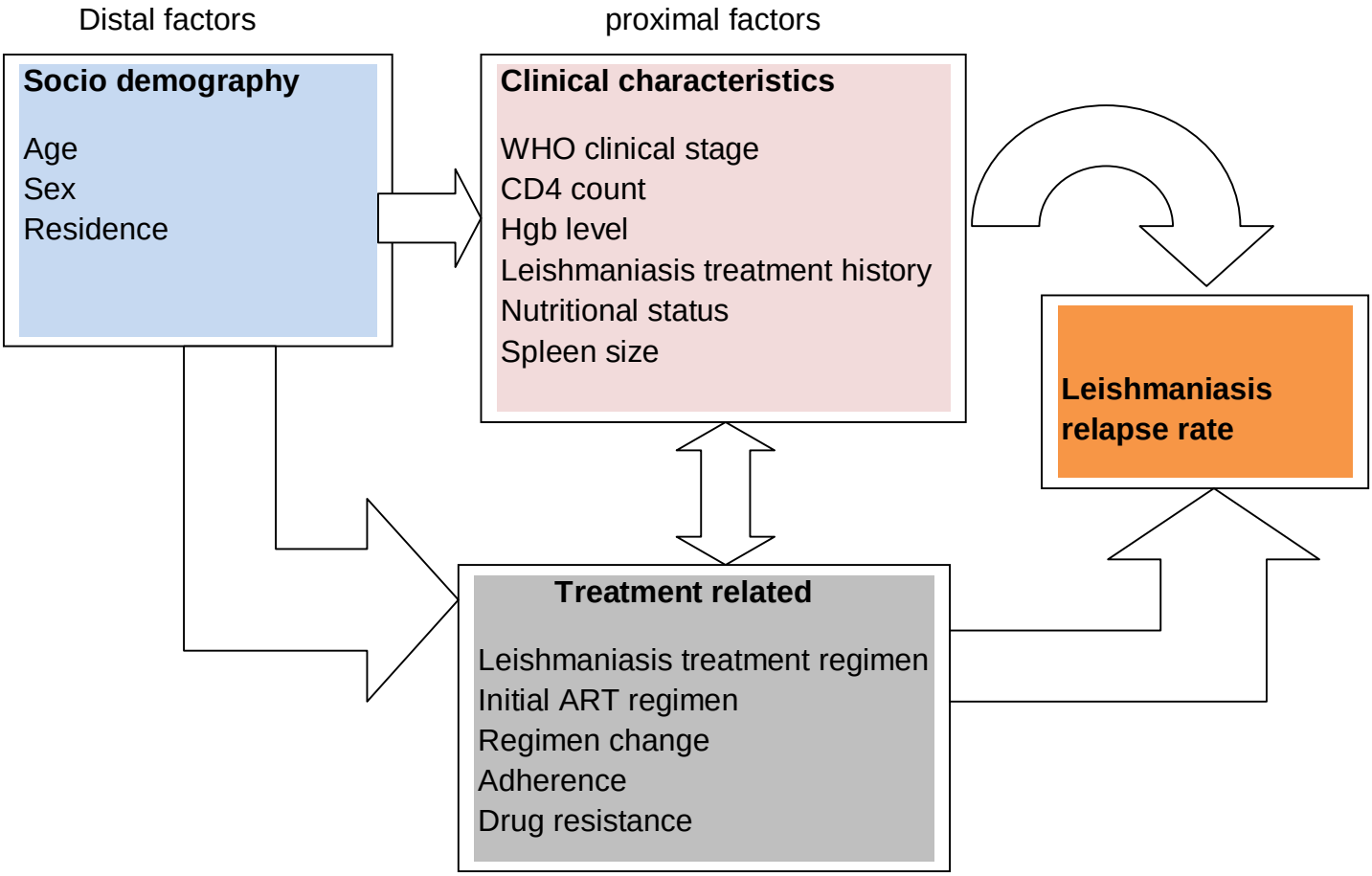

Figure. 1: Conceptual frame work for the occurrence of relapse of leishmaniasis among leishmaniasis/HIV co-infected on in leishmaniasis treatment center at MSF leishmaniasis treatment center in west Armachio district, January 2009 to December 2013.

1.4 Significance of the study

Leishmaniasis is the commonest cause of morbidity and mortality among PLHIV. It is also special in HIV infected patients because it increases the occurrence of relapse, other opportunistic infections and it occurs at various WHO clinical stage of HIV infection and it is fatal. In addition to this, unless we prevent in advance by identifying the potential risk factors, the anti-leishmaniasis treatment takes a long time unlike other opportunistic infection treatment which create a burden for those who are on HAART.

There are lots of challenges associated with VL treatment. Challenges may be related to the preparation of the available drugs, treatment choice and availability of the drugs .The drugs widely used are injectables, It is painful and very expensive, with high toxicity and less efficacy for HIV co-infected VL patients.

Therefore, this study will determine the factors that are responsible for relapse of Leishmaniasis diagnosis and treatment. And it will provide an input and directions to governmental policy makers and non-governmental organizations on Leishmaniasis treatment, prevention and control strategy. This study will be used as a base line for further study.

2. Objective

2.1 General objective

- To assess visceral leishmaniasis relapse rate among all visceral leishmaniasis patients in leishmaniasis treatment center at West Armachio, Northwest Ethiopia, 2014.

2.2 Specific objectives

- To determine the relapse rate of visceral leishmaniasis occurrence among visceral leishmaniasis patients.
- To identify the risk factors of relapse of visceral leishmaniasis occurrence among visceral leishmaniasis patients.

3. Methods

3.1 Study design

A five years institution based retrospective follow up study was conducted.

3.2 Study area and period

The study was conducted at West Armachio Leishmaniasis Treatment Center from March 25/ 2014 to April 15/ 2014. This Leishmaniasis treatment center is found in west Armachio Woreda, Its run by international nongovernmental organization of Medicines sans frontiers' located in North Gondar administrative zone, Amhara National Regional state, which is found at about 727 km Northwest of Addis Ababa (the capital city of Ethiopia).

According to the 2007 population and housing census report, the total population size of west Armachio Woreda was estimated which serves residents 35,486 people, of which female 15,969 and 19,517 male (population data from Woreda health office 2012) and Migrant workers, an average 300,000 less than 2% females and Settlers about 33,976 (22,341 male, 11,640 female).

The treatment center of leishmaniasis has one project coordinator, two expatriate medical doctors and one Ethiopian doctor for providing leishmaniasis and ART services, 4 Health officers , 4 BSc Nurse. And 13 Diploma nurses, 1 data clerks, 1porter, 2 janitors,3 case manager and 8 adherence supporters (people living with HIV). The treatment center uses standardized monitoring and evaluation tools and the data collection and management process is well controlled and supported by electronic data back-up and processing.

3.3 Source and Study Population

3.3.1 Source Population

All patients who have got Visceral Leishmaniasis in West Armachio Woreda were the source population.

3.3.2 Study Population

All patients who have visceral leishmaniasis relapse enrolled to leishmaniasis treatment center in West Armachio Woreda from January 2009 to December 2013 were the study population.

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion:

All charts of visceral leishmaniasis patients, who enrolled in the leishmaniasis treatment center from January 2009 to December 2013.

3.4.2 Exclusion:

Charts with incomplete documentation of patients history were excluded.

3.5 Sample size and sampling procedures

All charts of visceral leishmaniasis patients,who were registered from January 2009 to December 2013 at the leishmaniasis treatment center in West Armachio Woreda Medicines San Frontiers (MSF) project were included in the study.

3.6 Variables of the Study

3.6.1 Dependent variable:

Relapse of Visceral leishmaniasis

3.6.2 Independent variables:

- **Socio-demographic characteristics:** Age, Sex, Residence and Address.
- **Clinical characteristics:** WHO clinical Stage of HIV,CD4+ counts, Hemoglobin level (Hgb) at admission and at discharge time, spleen size at admission and discharge time, Nutritional status, Sero status, Tb co-infection,
- **Follow-up clinical and treatment related characteristics:** initial leishmaniasis regimen and duration, prior history of leishmaniasis, functional status**,** and treatment defaulter.

3.7 Operational definitions

Relapse: The reoccurrence of Visceral leishmaniasis in patients with HIV co-infection or no HIV co-infection after a full treatment regimen which is tested positive by spleenic aspiration, or bone marrow aspiration and identified by signs and symptoms.

Defaulter: A patient who fails to finish treatment of visceral leishmaniasis because of hepatotoxicity, cardio-toxicity or by other causes like co-infection of TB and concomitant infections.

Splenomeglay: A patient with an abnormal increment of the spleen size.

Anemia: The level of red blood cell count or hemoglobin (Hgb) of patients < 7 (1, 19)

Migrant - who travels seasonally, or has been to the site for less than two years. **Settler** - who have moved to the place and lived for more than two years.

Resident - who has been there for generations or (lived more than ten years).

3.8 Data Collection Tools and Procedures

The available information on the patient records were first observed and appropriate data extraction cheek list was prepared in English. Then the data was extracted by two nurses who are working in the health center using the prepared data collection cheek list. One data clerk also was supporting them by identifying the charts/ electronics. Charts/electronics were retrieved using the patients' registration numbers that are found in data base in the electronic system established by MSF-Holland.

3.9 Data quality control

Quality of data were maintained by recruiting data collectors who took ART and leishmaniasis diagnosis and treatment trainings. The data collectors were given intensive training for one day before the data collection on the objective of the study and how to retrieve data for this study purpose using the data extraction format. They were briefed on the definition of variables on the cheek list and registration charts. The retrieval process was closely monitored by the principal investigator throughout the data collection period. Completed forms were checked regularly for completeness of the information and any gaps identified were immediately communicated to the data collectors.

3.10 Data processing and analysis

After checking for completeness, the data were entered to excel then exported to SPSS version 20 for analysis. Data were entered by the principal investigator and clean before analysis.

Summary statistics was carried out to describe the demographics, base line and follow up data. Relapse density rate (RDR) was calculated for the entire study period. Life table was used to estimate the cumulative survival of relapse of leishmaniasis. Log rank test was used to compare survival probabilities between the different categories of the explanatory variables.

Both bivariate and multivariate Cox proportional hazard model was used to identify the predictors. Variables with p value <0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety five percent (95%) confidence interval of hazard ratio was computed and variables having p value < 0.05 in the multivariate Cox proportional hazards model was considered as significantly and independently associated with the dependent variable. The necessary assumptions of Cox proportional hazard model were checked by using schoenfield residuals test and graphically.

3.11 Ethical Consideration

Ethical clearance was obtained from the research review committee of the Institute of Public Health, University of Gondar. Permission of a written letter was obtained from Medicine San Frontiers medical team leaders and management teams of leishmaniasis treatment center. And oral permission also was obtained from data clerk focal person to use the secondary data for the purpose of this study. The name or any other identifying information were not recorded on the cheek list and all information taken from the chart/electronics was kept strictly confidential and in a safe place. The information retrieved was used only for the study purpose.

3.12 Dissemination of Results

The result was summated as partial fulfillment of the degree of Master of Public Health in epidemiology and biostatistics to the institute of Public Health, College of Medicine and Health Sciences, University of Gondar.

It will be also disseminated to Amhara regional Health bureau, North Gondar Health Department and nongovernmental organizations who are specially working on Leishmaniasis, HIV/AIDS and Malnutrition (medicine sans frontiers'). The result will be also presented at University of Gondar annual research conference, and other conferences and workshops. Moreover, the result will be sent for publication at scientific National or international journals.

4. Results:

4.1 Socio-demographic characteristics of Leishmaniasis patients

A total of 1676 records of Leishmaniasis pts who were enrolled from January 1, 2009 to December 31, 2013 were reviewed. of these 166 (10 %) were not included in the analysis due to missing of records. Among 1510 (90%) patients remaining in the analysis, 1450 (96 %) of Leishmaniasis patient were male. Almost half of 699(46.3%) of them were in the age group of 15-24 years and 530(35%) 25-34 years. The median age of the study participants was 24yrs.

Participants In west Armachio district 810 (53.6%) of the patients were residents while 564 (37.4 %) of them were migrant workers.

Table 1: Socio demographic characteristics of leishmaniasis patients at MSF leishmaniasis treatment center, January 1, 2009 to December 31, 2013.

Characteristics	Number	Percent
Age		
<=14yrs	108	7.2
15-24yrs	699	46.3
25-34yrs	530	35.1
>=35yrs	173	11.5
Sex		
Male	1450	96.0
Female	60	4.0
Residence		
Migrant worker	564	37.4
Resident	810	53.6
Settlers	136	9.0
Ethnicity		
Amhara	1342	88.9
Tigray	144	9.5
Oromia	16	1.1
Afar	8	.5

4.2 Clinical and immunological status of the study participants

Total eligible leishmaniasis patients had 1510 (90%), out of this 336 (22.2 %) of them were HIV/AIDS co-infected and 1174 (77.7%) were Non HIV/AIDS Primary kalazar patients, among those co-infected patients 186 (55.4%) of them were relapsed and 150 (44.6%) weren't relapsed. Among 1174 (77.7%) of PKA 49(4.1%) of them were relapsed the rest 1125(95.8%) weren't relapsed.

Out of 1510 leishmaniasis patients 128 (8.4%) of them were Tb co-infected, 55(42.9%) and 73(57%) of them were leishmaniasis relapse and non relapse respectively. In this study the discharge hemoglobin had highly significant which was <7mg/dl is 1328 (87.9%).

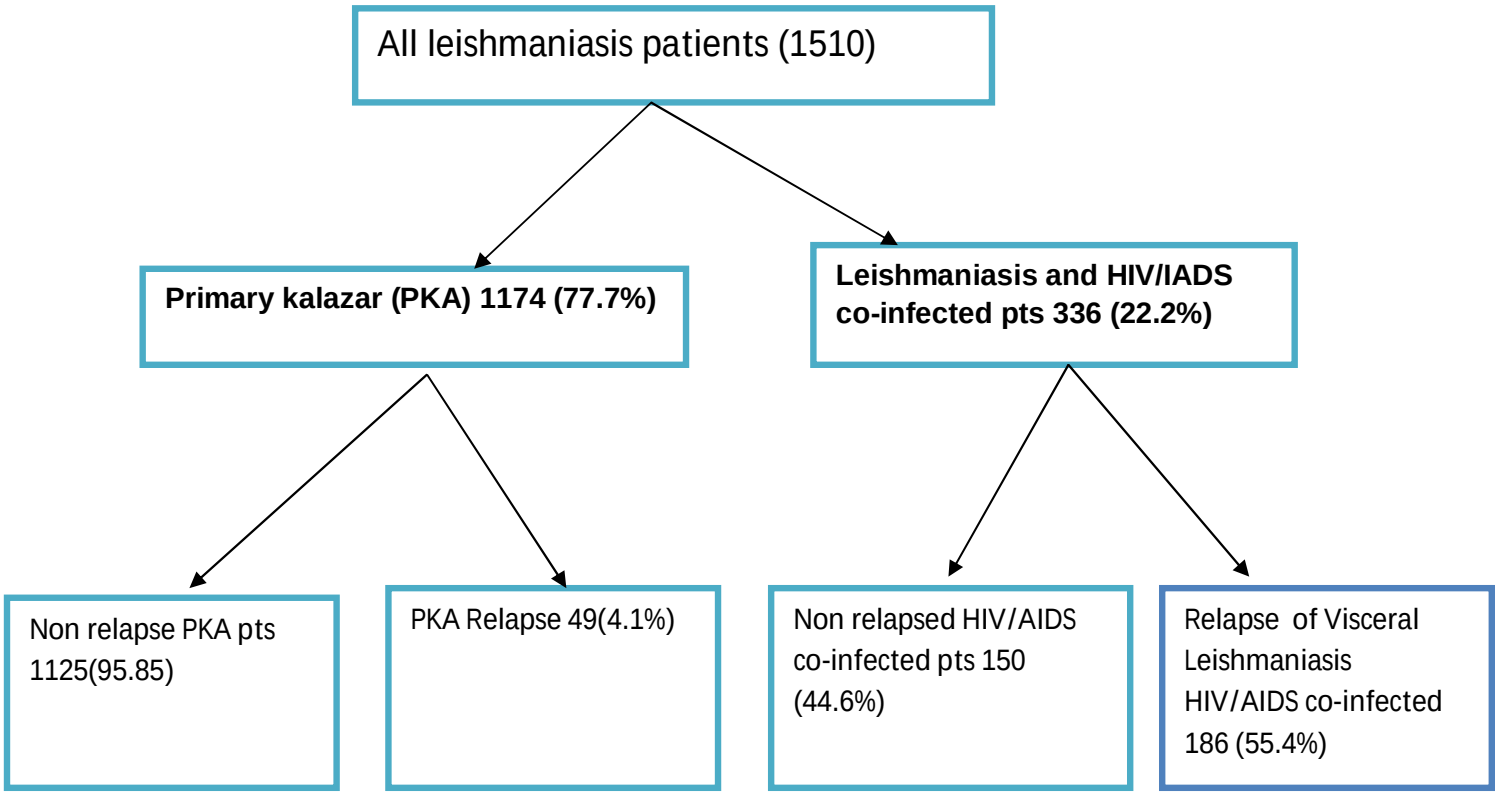

Figure : Clinical and immunological status of the study participants at MSF leishmaniasis treatment center in west Armachio district, January 1, 2009 to December 31, 2013.

Table 2: Clinical and immunological status of leishmaniasis patients and co-infected of HIV/AIDS at MSF leishmaniasis treatment center from January, 2009- December, 2013.

Characteristics	Number	Percent
Edema		
Yes	165	10.9
No	1345	89.1
Admition spleen size		
spleen size < =3 cm	1136	75.2
spleen size > 3cm	374	24.8
Admition Hgb		
Hgb <= 7 g/dl	1435	95.0
Hgb >7g/dl	75	5.0
Discharge spleen size		
spleen size < =3 cm	1444	95.6
spleen size > 3 cm	66	4.4
Discharge Hgb level		
Hgb <=7g/dl	1328	87.9
Hgb >7g/dl	182	12.1
Tb co infection		
Positive	128	8.5
Negative	1382	91.5
Sero status		
Positive	336	22.3
Negative	1174	77.7
CD4 count		
<200	156	46.4
>=200	56	16.6
Treatment type		
SSG	919	60.9
Ambisone	419	27.7
Ambisone + Meltifocin	172	11.4

4.3 Leishmaniasis Relapse Incidence density rate

Leishmaniasis relapse rate was classified based on socio-demographic and clinical characteristics. One thousand five hundred ten study individuals were followed for different periods for five years. Within the follow up period, 1275 (84.4%) new Leishmaniasis cases were observed. Hence, the overall Relapse rate was 235 (15.6%). The Study participants were followed for a minimum of 3 month and a maximum of 60 months.

The Incidence density rate of relapse among the age group of 15-24 and 25-34 was 4.3/10,000 person month and 15.5/10,000 person month respectively. And The Incidence density of discharge hgb < = 7mg/dl and hgb > 7mg/dl was 23.5 /10,000 person month and 8.7/10,000 person month respectively. The incidence density rate of Sero status of the study participant was 51.6/10,000n person month and 2.5/10,000 person month respectively. Total incidence density rate of relapse was 10/10,000 person month.

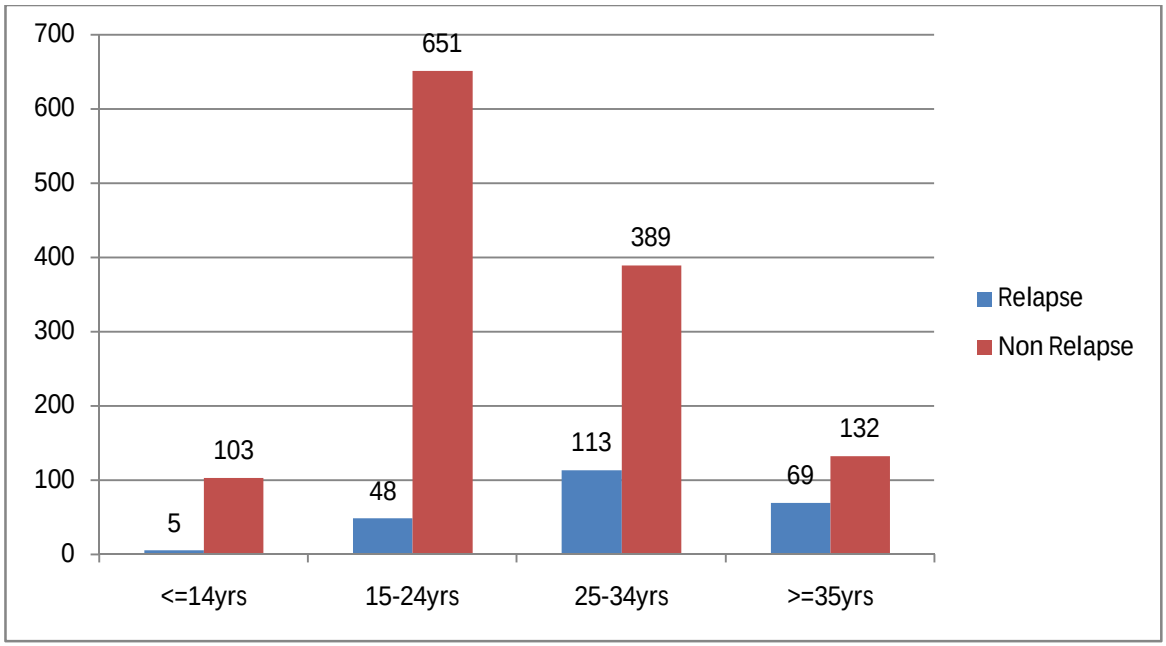

Figure 2: Relapse of leishmaniasis among the age groups at MSF leishmaniasis treatment center in west Armachio district, January 1, 2009 to December 31, 2013.

Table 3: Relapse incidence density rate stratified by socio-demographic and clinical characteristics of Leishmaniasis at MSF leishmaniasis treatment center from January, 2009- December, 2013.

Characteristics	Total	PM	Relapse case	Relapse IDR/10,000
Sex				
Male	1450	222960	229	10.2
Female	60	10899	6	5.5
Age				
<=14yrs	108	19722.0	5	2.5
15-24yrs	699	112351.5	48	4.2
25-34yrs	502	73056.0	113	15.5
>=35yrs	201	28729.5	69	24
Residence				
Migrant worker	564	85312.5	108	12.6
Resident	810	118278.0	121	10.2
Settlers	136	30268.5	6	1.98
Edema				
Yes	165	22704.0	55	24.2
No	1345	211155.0	80	3.7
Addmition spleen size				
spleen size <= 3 cm	1265	198303.0	205	10.3
spleen size > 3 cm	245	35556.0	30	8.4
Discharge spleen size				
spleen size < =3 cm	1462	226614.0	231	10.1
spleen size > 3 cm	48	7245.0	4	5.5
Addmition Hgb				
Hgb < 7mg/dl	465	60895.5	64	10.5
Hgb >= 7mg/dl	1045	172963.5	171	9.8
Discharge Hgb level				
Hgb <=7mg/dl	166	20356.5	48	23.5
Hgb > 7mg/dl	1344	213502.5	187	8.7
Tb co infection				
positive	128	16957.5	55	32.4
negative	1382	216901.5	180	8.29
Sero status				
positive	336	35820.0	185	51.6
negative	1174	198039.0	50	2.5
Treatment type				
SSG	808	159754.5	36	2.2
Ambisone	419	65968.5	83	12.5
Ambisone + Meltifocin	283	8136.0	116	14.5

PM (person month)

The cumulative probability of Leishmaniasis relapse of survival at the end of 3 month was 0.98; that of surviving at the end of 6 month was 0.90; that of surviving at the end of 9 month was 0.87 and that of surviving at the end of first year (12) month was 0.85.and that of surviving at the end of 24 month was 0.83; and that of surviving at the end of 45 month was 0.82; that of surviving at the end of 60 month was 0.82. The median survival time from enrolment to leishmaniasis relapse occurrence is 60 month.

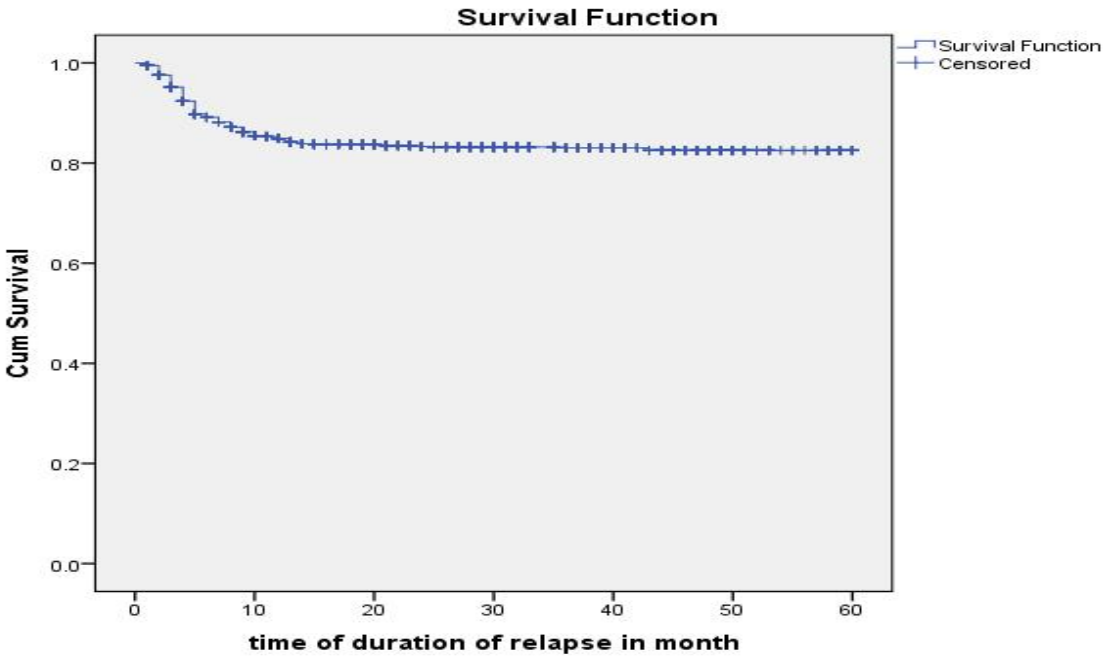

Figure 3: The cumulative survival proportion for leishmaniasis and HIV/AIDS Co-infected on MSF-H leishmaniasis treatment center at west Armachio, January 2009 to December 2013.

4.4 Factors of Leishmaniasis relapse occurrence

Log rank (Mantel-Cox) test of equality of survival for the different categories of explanatory variables, treatment type, Sero status, CD4 count and Discharge hgb level and Oedema were significantly associated with Relapse of leishmaniasis. The mean survival time of Relapse for those who had Sero status was 30.1and 57.4months respectively. The difference was significant at $p < 0.001$.

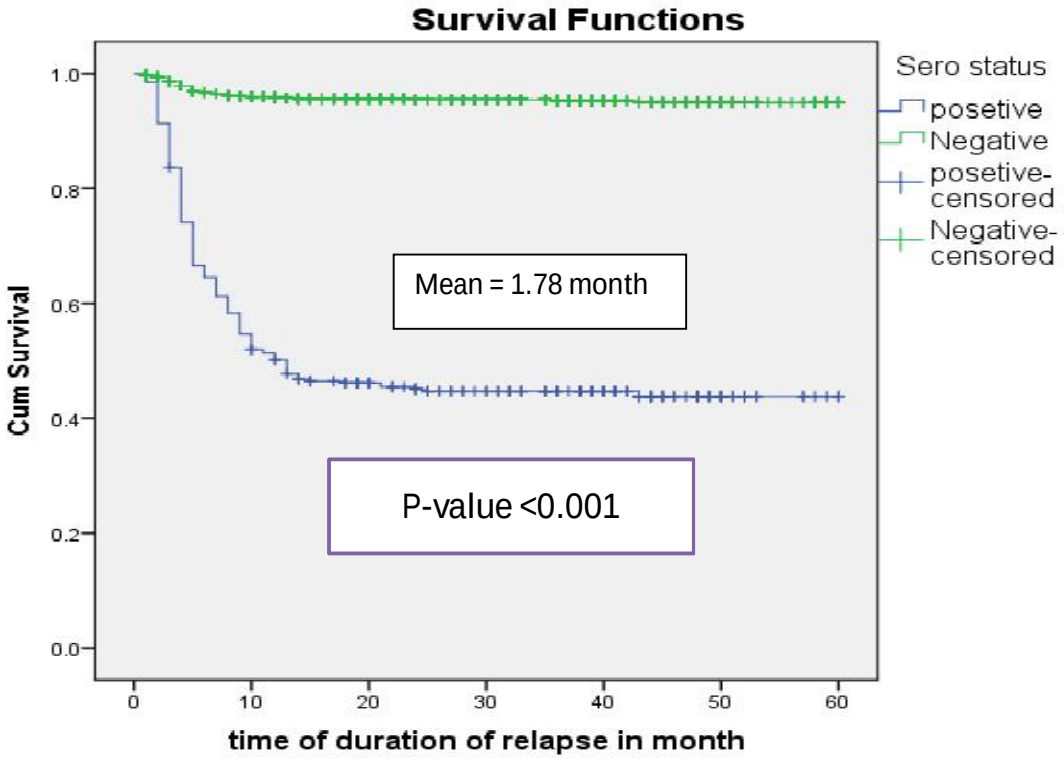

Figure 4: The relapse proportion based on Sero status among All leishmaniasis on MSF-H leishmaniasis treatment center at west Armachio, January 2009 to December, 2013.

The mean survival time of Relapse for those who had taking treatment of SSG, Ambisone and Ambisome+ Meltifocin was 57.5, 48.4 and 21.5 months respectively. The difference was significant at $p < 0.001$.

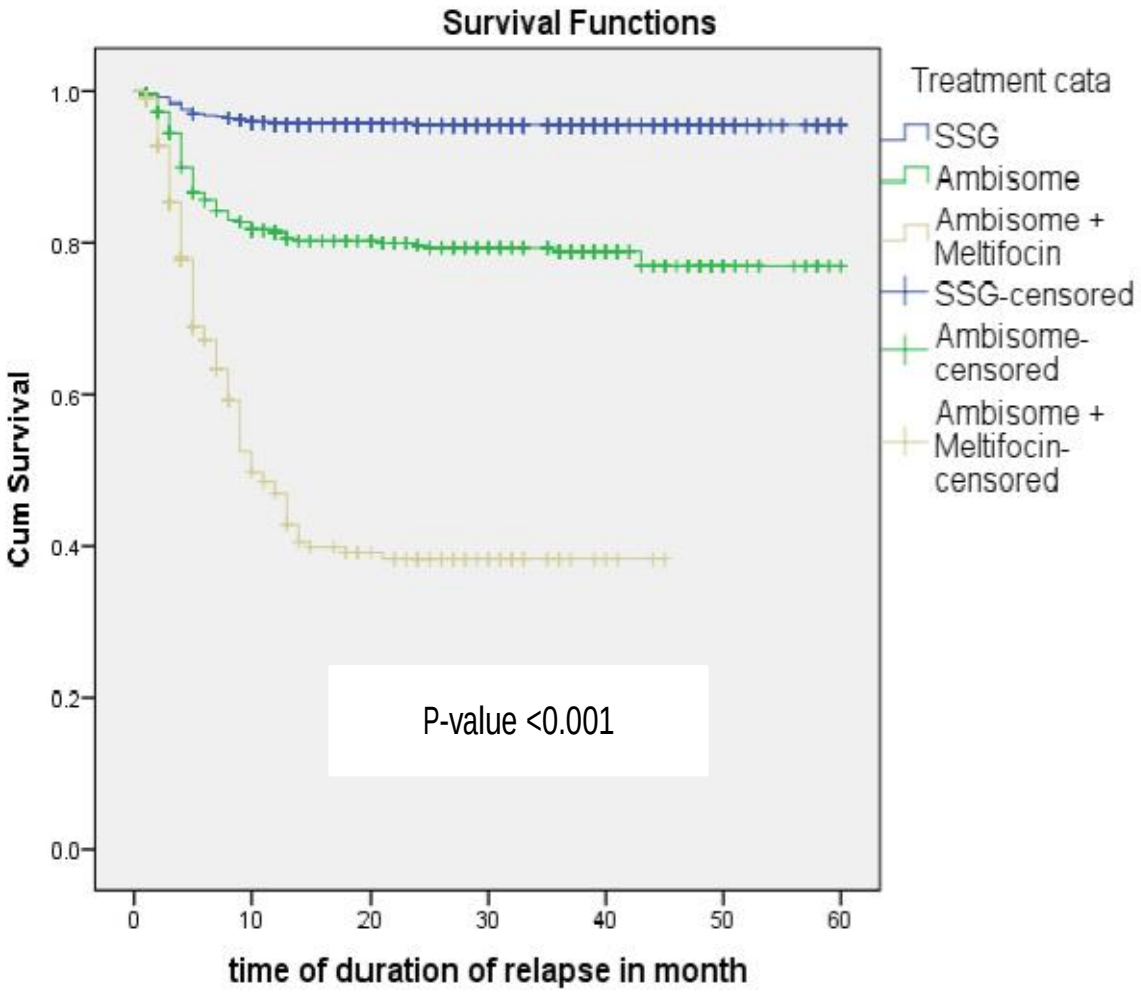

Figure 5: The relapse proportion based on Clinical treatment among All leishmaniasis and HIV/AIDS co-infected on MSF-H leishmaniasis treatment center at west Armachio, Jan 2009 to December, 2013.

The mean survival time of Relapse for those who had Discharge haemoglobin level<7mg/dl and >7mg/dl was 42.0, and 51.8 months respectively. The difference was significant at p < 0.001.

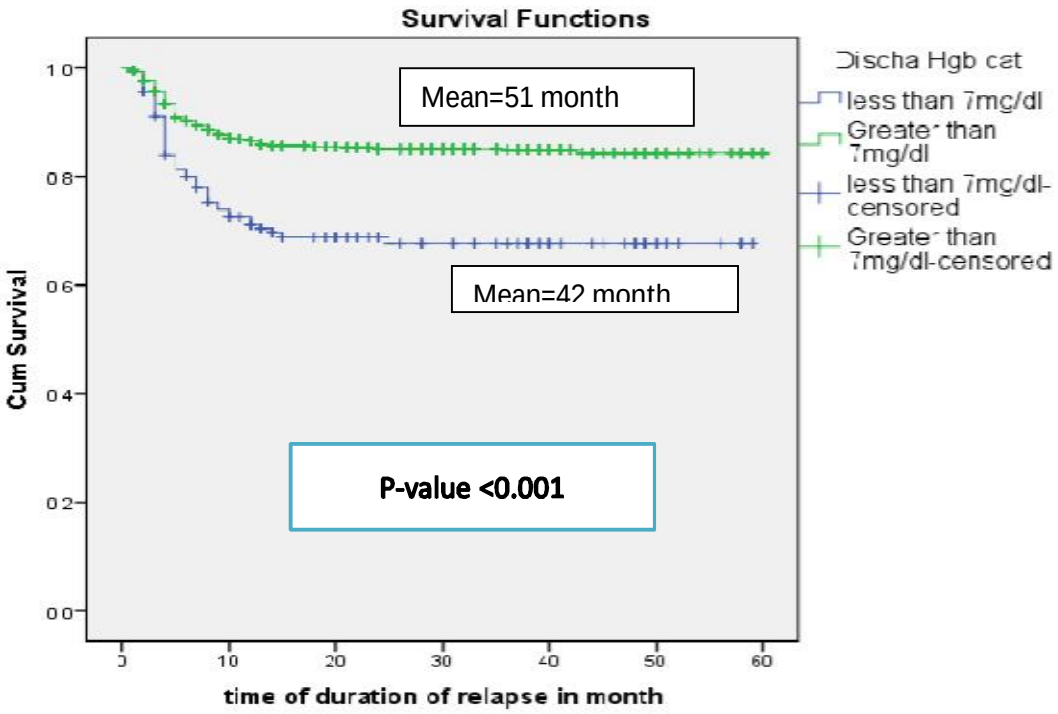

Figure 5: The relapse proportion based on Discharge hemoglobin level among All Visceral leishmaniasis and HIV/AIDS co-infected at MSF-H leishmaniasis treatment center at west Armachio, January 2009 to December, 2013.

4.5 Multivariate analyses of factors associated with visceral leishmaniasis relapse in HIV-positive and HIV-negative patients.

Findings from bivariate Cox-regression analysis showed that Age, residence Edema, Hemoglobin level, Tb co-infection, Sero status, baseline CD4 cell count, Baseline WHO clinical stage III and stage IV and drug used had association with Relapse of leishmaniasis with free survival time among people living with HIV/AIDS.

In the multivariate Cox-regression analysis, Edema, Sero status, CD4 cell count and WHO clinical stage, hemoglobin level, Treatment remained statistically significant predictors of time to Leishmaniasis relapse occurrence.

A patient with CD4 cell count greater than 200 cell/ul is 1.26 times late probably to have leishmaniasis relapse at any time than a patient with a CD4 cell count less than 200 cell/ul (AHR= 1.26,95% CI 0.85,1.87) respectively.

Those who were hemoglobin level >7mg/dl had late probablity to develop leishmaniasis relapse than hgb level less than 7 mg/dl. (AHR 0.69, 95% CI 0.49, 0.97).

Patients who were taking Ambisone and Ambisone +Meltifocin had less likely to develop relapse than a patient taking SSG. (AHR 2.62 CI 95% 1.72, 3.97) and AHR3.92 CI 95%2.51, 6.12) respectively.

Table 4: Clinical status of Leishmaniasis and HIV/AIDS co-infected patients on Leishmaniasis treatment center at MSF-Holland in west Armachio district January 1/2009 to December 31, 2013.

	Relapse of Kalazar			
Characteristics	Relapse	Non Relapse	CHR(95%CI)	AHR(95%CI)
Age				
<=14yrs	5	103	1	
15-24yrs	48	651	1.54 (0.62, 3.87)	
25-34yrs	113	389	5.19 (2.12,12.73)	
>=35yrs	69	132	8.29 (3.34 , 20.55)	
Residence				
Migrant worker	108	456	1	
Resident	121	689	0.79 (0.61 , 1.03)	
Settlers	6	130	0.20 (0.09 ,0.46)	
Discharge Hgb				
Hgb < =7mg/dl	48	118	1	1
Hgb >7mg/dl	187	1157	0.43 (0.32 ,0.59)	0.69 (0.49 ,0.97)
Tb co infection				
Positive	76	56	1	
Negative	1264	182	0.28 (0.21 , 0.38)	
Sero status				
Positive	185	151	1	1
Negative	50	1124	0.64 (0.05,0.09)	0.22(0.14, 0.37)
Clinical stage of HIV/AIDS				
stage II	12	16	1	1
stage III	29	12	2.87(1.36 ,6.08)	1.64(0.99 ,2.71)
Stage IV	121	94	2.11(1.07,4.15)	1.51 (1.03,2.21)
CD4 count				
<200	156	0	1	1
> 200	32	24	5.13 (3.53 , 7.46)	1.26 (0.85 ,1.87)
Treatment type				
SSG	36	772	1	1
Ambisone	83	336	5.17 (3.49 ,7.65)	2.62 (1.72 ,3.97)
Ambisone + Meltifocin	116	167	17.79 (12.19 , 25.99	3.92 (2.51 ,6.12)
Admition edema				
Yes	55	110	1	1
No	180	1165	0.39(0.29 ,0.53)	0.67(0.49,0.93)

5. Discussion

As seen from this study the predictors that were significantly associated with increased risk of relapse were HIV/AIDS Sero status, VL treatment, Discharge hemoglobin level and edema. All this predictors had already been identified in other studies.

This study revealed that treatment of VL had highly significant. Its inline with a study in Sudan, it suggests that a significant number of patients relapse 6–12 months post-treatment with mulitefosine and the relapse rates in immune competent patients of between 6.8% to 10.8% at 6 months respectively, and up to 20.0% at 12 months(7). In addition to this, other studies in ethiopia revealed that OR 6.53 95% CI 2.53,16.89) The reasons of these was all treatment type is toxic and painful and takes a longer period of time.

This study shows that 90% of the study participants were enrolled in the leishmaniasis treatment center and 15.6 % of them were VL relapsed. It is in line with Nepal, the Relapse rates in immune competent patients between 6.8% to 10.8% at 6 months respectively, and up to 20.0% at 12 months in Nepal (10)

This research work has also found that patients with baseline CD4 < 200 cells/ µl had 1.26 AHR(95% CI (0.85 ,1.87) times higher risk of developing relapse as compared to CD4baseline>200 cells/ µl. It is in line with In India. This could be due to the fact that patients became bed reddened or ambulatory as result of affected by many infectious diseases when their CD4 cell count is low. Baseline CD4 cell count of < 200 cells/ µl was a very strong and independent risk factor associated with a higher risk of VL relapse in patients enrolled to Leishmaniasis treatment center(10).

As seen in this study the spleen size is no significant for relapse of Visceral leishmaniasis ,but a study revealed in Sudan, the larger spleen size upon admission and at the time of discharge were strongly associated with relapse, as was treatment with a short-course combination treatment (17days sodium stibogluconate /paromomycin vs 30 days sodium stibogluconate). Age, sex, nutritional status, mobility, and treatment complications were significantly associated with relapse (2).

This research work has also found that patients with VL relapse had a risk of developing TB as compared to working functional status. Other studies in Ethiopia It has significant association with TB. The presence of TB and sepsis syndrome also remained significant in the multivariate analysis as independent factors in HIV co-infected patients with VL (AOR 4.52, 95% CI 1.47–13.92 and 9.06, 95% CI 2.16–37.97, respectively (14)

As revealed from this study Discharge hemoglobin level has highly significant for VL relapse. It is in lower than a study in Ethiopia. A total of 130／137 (94.9%) of HIV-negative and 69 (94.2%) of HIV-positive patients with hemoglobin measurements were anemic. Total white cell and platelet counts were available for 118 and 105 HIV-negative patients and 51 and 39 HIV-positive patients. Thrombocytopenia was more commonly seen in HIV-negative than co-infected patients (90.5% v 76.9%, OR = 2.85, 95% CI 1.06–7.67, P = 0.038.The reasons for lowered discharged Hgb level was because of the pathogenesis leishmaniasis infectivity of the vital organs (6).

As seen from this study HIV positive VL patients has significantly associated with relapse of visceral leishmaniasis, it is in line with other studies in Nepal, Sudan, and Ethiopia.

This study also showed that Edema has significantly associated with relapse of Visceral leishmaniasis. but other studies they didn’t identified it.

6. Limitation and strength of the study

Limitations:

Since it was based on secondary data some of the important predicators which had a significant association with Leishmaniasis relapse occurrence with other studies like body mass index were not included in the analysis due to incomplete registration of the charts.

Those study subjects whose charts lost weren't included in the study which may undermine the result if it is related with Leishmaniasis.

Strength:

The study was conducted for a long follow up (five years) period which enabled us to know the long term impact of leishmaniasis relapse at the treatment center.

7. Conclusions

Relapse rate of leishmaniasis was high among people living with HIV/AIDS especially in the first year of enrollment to the treatment center.

Relapse of leishmaniasis was effectively treated by Ambisone and meltefocin than SSG treatment on HIV/AIDS co-infected pts.

Advanced WHO clinical stage, and low CD4 (<200cell/ul) count, discharge hemoglobin level found to be the independent predictor of relapse leishmaniasis occurrence.

8. Recommendations

➢ **To governmental and nongovernmental organizations**

- Leishmaniasis and HIV/AIDS collaborative long term surveillance program should be strengthening at leishmaniasis endemic areas.
- Leishmaniasis prevention strategies need to be strengthened with early diagnosis and treatment as a recommended in national guideline

➢ **To Health care providers**

- Close follow-up and screening of patient especially with in the first year of enrollment to the treatment center.
- It would be better to give special attention for ambulatory or Bed redden, WHO clinical stage III or IV and people with low (<200 cell/ul) CD4 cell count to diagnose, prevent and treat leishmaniasis early.

➢ **For the patients**

- Early seek of health care; enrolled to the treatment center and taking ART have great importance to reduce the risk of Relapse.

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1. Annex

Annex 1 - Information Sheet

Title of the Research Project: Assessment of Visceral leishmaniasis relapse among al leishmaniasis patients and HIV co infected patients in west Armachio Woreda North west Ethiopia, retrospective study of risk factors.

Name of Investigator: Zelalem Mekonnen (Bsc in clinical Nurse)

Name of the Organization: University of Gondar College of Medicine and Health Sciences, Institute of Public Health.

Name of the Sponsor: self sponsor.

Introduction: this information sheet is prepared for North Gondar zonal BOH, west Armachio Woreda BOH and leishmaniasis treatment project center team leaders Medicine sans frontiers' (MSF) coordinating office. The aim of the form is to make the above concerned office clear about the purpose of research, data collection procedures and get permission to conduct the research.

Purpose of the Research Project: To Evaluate the level of Visceral leishmaniasis relapse rate among all leishmaniasis patients and HIV co infected patients in leishmaniasis treatment center at west Armachio, Northwest Ethiopia, retrospective study of risk factors, from January, 2009 to December, 2013.

Procedure: In order to achieve the above objective, information which is necessary for the study will be taken from leishmaniasis treatment center medical record follow up forms.

Risk and /or Discomfort: The study will be conduct by taking appropriate information from medical chart, it will not inflict any harm on the patients. The name or any other identifying information will not be record on the questionnaire and all information taken from the chart will be kept strictly confidential and in a safe place. The information retrieved will only be used for the study purpose.

Benefits: the research have no direct benefit for one whose document/ record is included in this research. But the indirect benefit of the research for the participant and other clients in the program is clear. This is because if program planners are preparing predict a plan, there is a benefit for clients in the program of getting appropriate care and treatment services. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on HIV/leishmaniasis co- infected collaborative program planning and management**.**

Confidentiality: to reassure confidentiality the data on the chart will be collect by those Nurses who are working in the leishmaniasis treatment project center and information will be collect without the name of the clients. The information collect from this research project will be kept confidential and will be store in a file. In addition, it will not be revealed to anyone except the investigator and it will be kept in key and locked system with computer pass ward.

Person to contact: This research project will be review and approve by the institutional review board of College of Medicine and Health Science, University of Gondar. If you want to know more information, you can contact the committee through the address below. If you have any question you can contact any of the following individuals (Investigator and Advisors) and you may ask at any time you want.

1. Zelalem Mekonnen, University of Gondar, College of Medicine and Health Science, Department of public Health: principal investigator
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   E-mail: zelamekon@gmail.com
2. Mekuriaw Alemayehu (Bsc, MSc) University of Gondar, College of Medicine and Health Science, institute of Public Health:Environmental and Occupational Health and safety: Advisor Cell phone: +251-09 20 51 00 50E-mail: mekuriaw04@gmail.com
3. Tesfahun Melese (MPH)University of Gondar, College of Medicine and Health Science, institute of Public Health: Advis
   Cell phone: +251- 918- 77-98-20 E-mail: tesfahunmelese@gmail.com

Annex 2- Data collection tool

Questionnaire prepared for collection of data on the patients ART or/and pre ART medical registration book/chart to assess the relapse of Visceral leishmaniasis among people living with HIV attending in HIV care clinic at Medicine sans frontiers' treatment center.

Code No._____

S. N.	Part I: Socio demographic characteristics		Skip to Qn
101	Date of enrolment	/ / /DD/MM/YY	
102	Age at enrolment	year	
103	Sex	1. Male 2. Female	
104	Marital status	1. Never married/ single 2. Married 3. Separated 4. divorced 5. Widowed/er 6. Others (specify)----------	
105	Level of education	1. No education 2. Primary (Grade 1- 8) 3. Secondary (Grade 9-10) 4. Preparatory (Grade 11-12) 5. Diploma level 6. Degree level 7. Not recorded	
106	Religion	1. Orthodox 2. Muslim 3. Protestant 4. Catholic 5. Others (specify) ----------	

107	Occupation	_____	
108	Address	1. Urban 2. Rural 3. Not recorded	
	Part II: Past Leishmaniasis treatment& other history		
201	Did the patient had past leishmaniasis treatment history?	1. Yes 3. Not recorded 2. No	
202	Is the treatment completed?	1. Yes 2. No	
203	Number of house hold	_____persons	
204	Height	_____Cm	
205	Weight	_____Cm	
	Part III: HIV care/ ART follow up		
301	Date confirmed HIV+	// (DD/MM/YY)	
302	ART Eligible date	// (DD/MM/YY)	
303	Eligible criteria	1. CD4 cell count 3. Both 2. WHO clinical stage 4. Not recorded	
304	Date ART started	// (DD/MM/YY)	
305	When was it changed	//(DD/MM/YY)& month ---------	
306	New regiment		
307	Reason for switch	1. Side effects 3. leishmaniasis 2. Pregnancy 4. Others ---------- --------	
308	Current status of VL pts	1.Alive 2.Dead 3.Relapsed 4.Defoulted 5.Drug resistance	

309	CD4 count	---------- cells	
310	Stage of HIV/AIDS	1. Satge I	
		2. Stage II	
		3. Stage III	
		4. Stage IV	
311	Admition spleen size	----------cm	
312	Discharge spleen size	----------cm	
313	Admition hemoglobin level	----------g/dl	
314	Discharge hemoglobin level	----------g/dl	
315	Did the patient develop leishmaniasis after treatment	1. Yes 2. No	
316	When was it developed?	/ / DD/MM/YY	
317	During what was it developed?	1. Pre ART 2. ART	
318	What type of leishmaniasis was it?	Visceral leishmaniasis ☐ Cutaneous leishmaniasis ☐	
319	Which type of drug used for primary VL treatment?	Ambisone ☐ ntamidin ☐ SSG ☐ paranomici ☐ Meltifocin ☐	
320	Which type of drug used after relapse of VL?	Ambisone ☐ ntamidin ☐ SSG ☐ paranomici ☐ Meltifocin ☐	

Annex 3-WHO HIV clinical staging criteria

1. **WHO Staging System for HIV Infection and Disease in Adults and Adolescents**

Clinical Stage	Clinical Description	Performance Scale
I	Asymptomatic Persistent generalized lymphadenopathy	1: Normal Activity
II	Weight loss <10% Minor symptoms and infections	2: Normal activity
III	Weight loss >10% Symptomatic Diarrhoea/fever >1 month	3: Bedridden >50% of days/month
IV	Symptomatic AIDS-Wasting syndrome Severe opportunistic infections	4: Bedridden ?50% of days/month

2. **Detailed description of the clinical stages of HIV/AIDS**

Clinical stage 1: a person with confirmed HIV infection who isasymptomatic and/or Persistent generalized lymphadenopathy (PGL)

Clinical stage 2: Apersonwith confirmed HIV infection and having:

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Popular pruritic eruptions

- Seborrhoeic dermatitis
- Fungal nail infections of fingers

Clinical stage 3: Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations:

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical stage 4: *Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations:*

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- HIV wasting syndrome
- Pneumocystis Carinii pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extra pulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Annex 4: Declaration

I, the undersigned, senior MPH student declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master of Public Health in Epidemiology and Biostatistics.

Student's Name: Zelalem Mekonnen

Signature: _____

Place of submission: institute of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This thesis proposal work has been submitted for examination with our approval as University advisor(s).

Advisors' Name	Date	Signature
1. Mr. Mekuriaw Alemayehu (Bsc, MSc)	----------	----------
2. Mr. Tesfahun Melese (BSc. MPH)	----------	----------

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